Omicron infection enhances neutralizing immunity against the Delta variant

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Omicron has been shown to be highly transmissible and have extensive evasion of neutralizing antibody immunity elicited by vaccination and previous SARS-CoV-2 infection. Omicron infections are rapidly expanding worldwide often in the face of high levels of Delta infections. Here we characterized developing immunity to Omicron and investigated whether neutralizing immunity elicited by Omicron also enhances neutralizing immunity of the Delta variant. We enrolled both previously vaccinated and unvaccinated individuals who were infected with SARS-CoV-2 in the Omicron infection wave in South Africa soon after symptom onset. We then measured their ability to neutralize both Omicron and Delta virus at enrollment versus a median of 14 days after enrollment. Neutralization of Omicron increased 14-fold over this time, showing a developing antibody response to the variant. Importantly, there was an enhancement of Delta virus neutralization, which increased 4.4-fold. The increase in Delta variant neutralization in individuals infected with Omicron may result in decreased ability of Delta to re-infect those individuals. Along with emerging data indicating that Omicron, at this time in the pandemic, is less pathogenic than Delta, such an outcome may have positive implications in terms of decreasing the Covid-19 burden of severe disease.

The Omicron variant of SARS-CoV-2, first identified in November 2021 in South Africa and Botswana, has been shown by us[1] and others[2-7] to have extensive but incomplete escape from immunity elicited by vaccines and previous infection, with boosted individuals showing effective neutralization, even though vaccine and booster efficacy may wane over time

(https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1043807/technical-briefing-33.pdf). In South Africa Omicron infections led to a lower incidence of severe disease relative to other variants[8], although this can be at least partly explained by pre-existing immunity[1]. While Omicron infections are rising steeply, many countries still have high levels of infection with the Delta variant. How Delta and Omicron will interact is still unclear, and one possibility is that Omicron will curtail the spread of Delta by eliciting a neutralizing immune response against Delta in people infected by Omicron.

We investigated whether Omicron infection elicits neutralizing immunity to the Delta variant. We isolated Omicron virus without the R346K mutation from an infection in South Africa. This virus had similar neutralization escape (Fig S1) as a previous Omicron isolate with the R346K mutation[1]. We neutralized this isolate with plasma from the blood of 15 participants enrolled during the Omicron infection wave in South Africa, with each participant having a confirmed diagnosis of SARS-CoV-2 by qPCR. To quantify neutralization, we used a live virus neutralization assay and calculated the focus reduction neutralization test ($FRNT_{50}$) value, the inverse of the plasma dilution required for 50% reduction in infection foci. The majority infecting viruses from the enrolled participants were successfully sequenced and all of these were Omicron (Table S1).

Eleven out of 15 participants were admitted to hospital because of Covid-19 symptoms, but none required supplemental oxygen. Participants were sampled at enrollment, which was a median of 4 days post-symptom onset and again at a median of 14 days post-enrollment. Two participants did not detectably neutralize Omicron at either timepoint and were excluded from the analysis. Two of the remaining 13 participants did not have detectable SARS-CoV-2 at enrollment, indicating that infection was already cleared, and therefore that these participants were sampled later post-infection. Out of the 13 participants, 7 were vaccinated, 3 with two doses of Pfizer-BNT162b2 and 4 with Johnson and Johnson Ad26.CoV2.S (Table S1) with one of the Ad26.CoV2.S vaccines being boosted with a second Ad26.CoV2.S dose.

We measured neutralization at enrollment and the later visit and observed that Omicron neutralization increased from a low geometric mean (GMT) $FRNT_{50}$ of 20 to 285, a 14.4-fold increase (95% CI 5.5-37.4, Fig 1A). Importantly, neutralization of Delta increased during this period 4.4-fold (95% CI 2.1-9.2), from $FRNT_{50}$ of 80 to 354 (Fig 1B). The two participants who were likely sampled at a longer time post-infection showed relatively high neutralization values at enrollment both against Omicron and Delta virus, and these did not appreciably increase with time, indicating that neutralization capacity plateaued before enrollment. Comparing Omicron and Delta neutralization at the last available timepoint showed that vaccinated participants were able to mount a better neutralizing response against Delta virus, while the response in unvaccinated participates was more variable (Fig 1C).

The ability of one variant to elicit immunity which can cross-neutralize another variant varies by variant[9-11]. Immunity elicited by Delta infection does not cross-neutralize Beta virus and Beta elicited immunity does not cross-neutralize Delta well[12,13]. However, participants in this study have likely been previously infected, and more than half were vaccinated. Therefore, it is unclear if what we observe is effective cross-neutralization of Delta virus by Omicron elicited antibodies, or activation of antibody immunity from previous infection and/or vaccination.

These results are consistent with Omicron displacing the Delta variant, since it can elicit immunity which neutralizes Delta making re-infection with Delta less likely. In contrast, Omicron escapes neutralizing immunity elicited by Delta[6] and therefore may re-infect Delta infected individuals. The implications of such displacement would depend on whether Omicron is indeed less pathogenic than Delta. If so, then the incidence of Covid-19 severe disease would be reduced and the infection may shift to become less disruptive to individuals and society.

Materials and methods

Informed consent and ethical statement

Blood samples were obtained after written informed consent from adults with PCR-confirmed SARS-CoV-2 infection who were enrolled in a prospective cohort study approved by the Biomedical Research Ethics Committee at the University of KwaZulu–Natal (reference BREC/00001275/2020). Use of residual swab sample was approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) (ref. M210752).

Data availability statement

Sequence of outgrown virus has been deposited in GISAID with accession EPI_ISL_7886688. Raw images of the data are available upon reasonable request.

Code availability

Image analysis and curve fitting scripts in MATLAB v.2019b are available on GitHub (https://github.com/sigallab/NatureMarch2021).

Whole-genome sequencing, genome assembly and phylogenetic analysis

RNA was extracted on an automated Chemagic 360 instrument, using the CMG-1049 kit (Perkin Elmer, Hamburg, Germany). The RNA was stored at −80◦C prior to use. Libraries for whole genome sequencing were prepared using either the Oxford Nanopore Midnight protocol with Rapid Barcoding or the Illumina COVIDseq Assay. For the Illumina COVIDseq assay, the libraries were prepared according to the manufacturer's protocol. Briefly, amplicons were tagmented, followed by indexing using the Nextera UD Indexes Set A. Sequencing libraries were pooled, normalized to 4 nM and denatured with 0.2 N sodium acetate. A 8 pM sample library was spiked with 1% PhiX (PhiX Control v3 adaptor-ligated library used as a control). We sequenced libraries on a 500-cycle v2 MiSeq Reagent Kit on the Illumina MiSeq instrument (Illumina). On the Illumina NextSeq 550 instrument, sequencing was performed using the Illumina COVIDSeq protocol (Illumina Inc, USA), an amplicon-based next-generation sequencing approach. The first strand synthesis was carried using random hexamers primers from Illumina and the synthesized cDNA underwent two separate multiplex PCR reactions. The pooled PCR amplified products were processed for tagmentation and adapter ligation using IDT for Illumina Nextera UD Indexes. Further enrichment and cleanup was performed as per protocols provided by the manufacturer (Illumina Inc). Pooled samples were quantified using Qubit 3.0 or 4.0 fluorometer (Invitrogen Inc.) using the Qubit dsDNA High Sensitivity assay according to manufacturer's instructions. The fragment sizes were analyzed using TapeStation 4200 (Invitrogen). The pooled libraries were further normalized to 4nM concentration and 25 µL of each normalized pool containing unique index adapter sets were combined in a new tube. The final library pool was denatured and neutralized with 0.2N sodium hydroxide and 200 mM Tris-HCL (pH7), respectively. 1.5 pM sample library was spiked with 2% PhiX. Libraries were loaded onto a 300-cycle NextSeq 500/550 HighOutput Kit v2 and run on the Illumina NextSeq 550 instrument (Illumina, San Diego, CA, USA). For Oxford Nanopore sequencing, the Midnight primer kit was used as described by Freed and Silander55. cDNA synthesis was performed on the extracted RNA using LunaScript RT mastermix (New England BioLabs) followed by gene-specific multiplex PCR using the Midnight Primer pools which produce 1200bp amplicons which overlap to cover the 30-kb SARS-CoV-2 genome. Amplicons from each pool were pooled and used neat for barcoding with the Oxford Nanopore Rapid Barcoding kit as per the manufacturer's protocol. Barcoded samples were pooled and bead-purified. After the bead clean-up, the library was loaded on a prepared R9.4.1 flow-cell. A GridION X5 or MinION sequencing run was initiated using MinKNOW software with the base-call setting switched off. We assembled paired-end

and nanopore.fastq reads using Genome Detective 1.132 (https://www.genomedetective.com) which was updated for the accurate assembly and variant calling of tiled primer amplicon Illumina or Oxford Nanopore reads, and the Coronavirus Typing Tool56. For Illumina assembly, GATK HaploTypeCaller --min-pruning 0 argument was added to increase mutation calling sensitivity near sequencing gaps. For Nanopore, low coverage regions with poor alignment quality (<85% variant homogeneity) near sequencing/amplicon ends were masked to be robust against primer drop-out experienced in the Spike gene, and the sensitivity for detecting short inserts using a region-local global alignment of reads, was increased. In addition, we also used the wf_artic (ARTIC SARS-CoV-2) pipeline as built using the nextflow workflow framework57. In some instances, mutations were confirmed visually with .bam files using Geneious software V2020.1.2 (Biomatters). The reference genome used throughout the assembly process was NC_045512.2 (numbering equivalent to MN908947.3). For lineage classification, we used the widespread dynamic lineage classification method from the 'Phylogenetic Assignment of Named Global Outbreak Lineages' (PANGOLIN) software suite (https://github.com/hCoV-2019/pangolin)19. P2 stock was sequenced and confirmed Omicron with the following substitutions: E:T9I,M:D3G,M:Q19E,M:A63T,N:P13L,N:R203K,N:G204R,ORF1a:K856R,ORF1a:L2084I,ORF1a:A2710T, ORF1a:T3255I,ORF1a:P3395H,ORF1a:I3758V,ORF1b:P314L,ORF1b:I1566V,ORF9b:P10S,S:A67V,S:T95I ,S:Y145D,S:L212I,S:G339D,S:S371L,S:S373P,S:S375F,S:K417N,S:N440K,S:G446S,S:S477N,S:T478K,S:E4 84A,S:Q493R,S:G496S,S:Q498R,S:N501Y,S:Y505H,S:T547K,S:D614G,S:H655Y,S:N679K,S:P681H,S:N76 4K,S:D796Y,S:N856K,S:Q954H,S:N969K,S:L981F. Sequence was deposited in GISAID, accession: EPI_ISL_7886688.

Cells

Vero E6 cells (ATCC CRL-1586, obtained from Cellonex in South Africa) were propagated in complete growth medium consisting of Dulbecco's Modified Eagle Medium (DMEM) with 10% fetal bovine serum (Hyclone) containing 10mM of HEPES, 1mM sodium pyruvate, 2mM L-glutamine and 0.1mM nonessential amino acids (Sigma-Aldrich). Vero E6 cells were passaged every 3–4 days. H1299 cell lines were propagated in growth medium consisting of complete Roswell Park Memorial Institute (RPMI) 1640 medium with 10% fetal bovine serum containing 10mM of HEPES, 1mM sodium pyruvate, 2mM L-glutamine and 0.1mM nonessential amino acids. H1299 cells were passaged every second day. The H1299-E3 (H1299-ACE2, clone E3) cell line was derived from H1299 (CRL-5803) as described in our previous work[9] and Figure S1. Briefly, vesicular stomatitis virus G glycoprotein (VSVG) pseudotyped lentivirus containing hACE2 was used to spinfect H1299 cells. ACE-2 transduced H1299 cells (containing an endogenously yellow fluorescent protein labelled histone H2AZ gene[14]) were then subcloned at the single cell density in 96-well plates (Eppendorf) in conditioned media derived from confluent cells. After 3 weeks, wells were detached using a 0.25% trypsin-EDTA solution (Gibco) and plated in two replicate plates, where the first plate was used to determine infectivity and the second was stock. The first plate was screened for the fraction of mCherry positive cells per cell clone upon infection with a SARS-CoV-2 mCherry expressing spike pseudotyped lentiviral vector. Screening was performed using a Metamorph-controlled (Molecular Devices, Sunnyvale, CA) Nikon TiE motorized microscope (Nikon Corporation, Tokyo, Japan) with a 20x, 0.75 NA phase objective, 561 nm laser line, and 607 nm emission filter (Semrock, Rochester, NY). Images were captured using an 888 EMCCD camera (Andor). The clone with the highest fraction of mCherry expression was expanded from the stock plate and denoted H1299-E3. Infectivity was confirmed with mCherry expressing lentivirus by flow cytometry using a BD Fortessa instrument and analyzed using BD FACSDiva Software (BD Biosciences). This clone was used in the outgrowth and focus forming assay. Cell lines have not been authenticated. The cell lines have been tested for mycoplasma contamination and are mycoplasma negative.

Virus expansion

All work with live virus was performed in Biosafety Level 3 containment using protocols for SARS-CoV-2 approved by the Africa Health Research Institute Biosafety Committee. ACE2-expressing H1299-E3 cells were seeded at 4.5×10^5 cells in a 6 well plate well and incubated for 18–20 h. After one DPBS wash, the sub-confluent cell monolayer was inoculated with 500 µL universal transport medium diluted 1:1 with growth medium filtered through a 0.45-µm filter. Cells were incubated for 1 h. Wells were then filled with 3 mL complete growth medium. After 4 days of infection (completion of passage 1 (P1)), cells were trypsinized, centrifuged at 300 rcf for 3 min and resuspended in 4 mL growth medium. Then all infected cells were added to Vero E6 cells that had been seeded at 2×10^5 cells per mL, 20mL total, 18–20 h earlier in a T75 flask for cell-to-cell infection. The coculture of ACE2-expressing H1299-E3 and Vero E6 cells was incubated for 1 h and the flask was then filled with 20 mL of complete growth medium and incubated for 4 days. The viral supernatant (passage 2 (P2) stock) was used for experiments.

Live virus neutralization assay

H1299-E3 cells were plated in a 96-well plate (Corning) at 30,000 cells per well 1 day pre-infection. Plasma was separated from EDTA-anticoagulated blood by centrifugation at 500 rcf for 10 min and stored at −80 °C. Aliquots of plasma samples were heat-inactivated at 56 °C for 30 min and clarified by centrifugation at 10,000 rcf for 5 min. Virus stocks were used at approximately 50-100 focus-forming units per microwell and added to diluted plasma. Antibody–virus mixtures were incubated for 1 h at 37 °C, 5% CO2. Cells were infected with 100 µL of the virus–antibody mixtures for 1 h, then 100 µL of a 1X RPMI 1640 (Sigma-Aldrich, R6504), 1.5% carboxymethylcellulose (Sigma-Aldrich, C4888) overlay was added without removing the inoculum. Cells were fixed 18 h post-infection using 4% PFA (Sigma-Aldrich) for 20 min. Foci were stained with a rabbit anti-spike monoclonal antibody (BS-R2B12, GenScript A02058) at 0.5 µg/mL in a permeabilization buffer containing 0.1% saponin (Sigma-Aldrich), 0.1% BSA (Sigma-Aldrich) and 0.05% Tween-20 (Sigma-Aldrich) in PBS. Plates were incubated with primary antibody overnight at 4 °C, then washed with wash buffer containing 0.05% Tween-20 in PBS. Secondary goat anti-rabbit HRP conjugated antibody (Abcam ab205718) was added at 1 µg/mL and incubated for 2 h at room temperature with shaking. TrueBlue peroxidase substrate (SeraCare 5510-0030) was then added at 50 µL per well and incubated for 20 min at room temperature. Plates were imaged in an ImmunoSpot Ultra-V S6-02-6140 Analyzer ELISPOT instrument with BioSpot Professional built-in image analysis (C.T.L).

Statistics and fitting

All statistics and fitting were performed using custom code in MATLAB v.2019b. Neutralization data were fit to:

$$Tx=1/1+(D/ID_{50}).$$

Here Tx is the number of foci normalized to the number of foci in the absence of plasma on the same plate at dilution D and ID_{50} is the plasma dilution giving 50% neutralization. $FRNT_{50} = 1/ID_{50}$. Values of $FRNT_{50} <1$ are set to 1 (undiluted), the lowest measurable value. We note that the most concentrated plasma dilution was 1:25 and therefore $FRNT_{50} < 25$ were extrapolated. We have marked these values in Figure 1C and calculate the fold-change $FRNT_{50}$ either for the raw values or for values where $FRNT_{50} > 25$ in Figure 1D.

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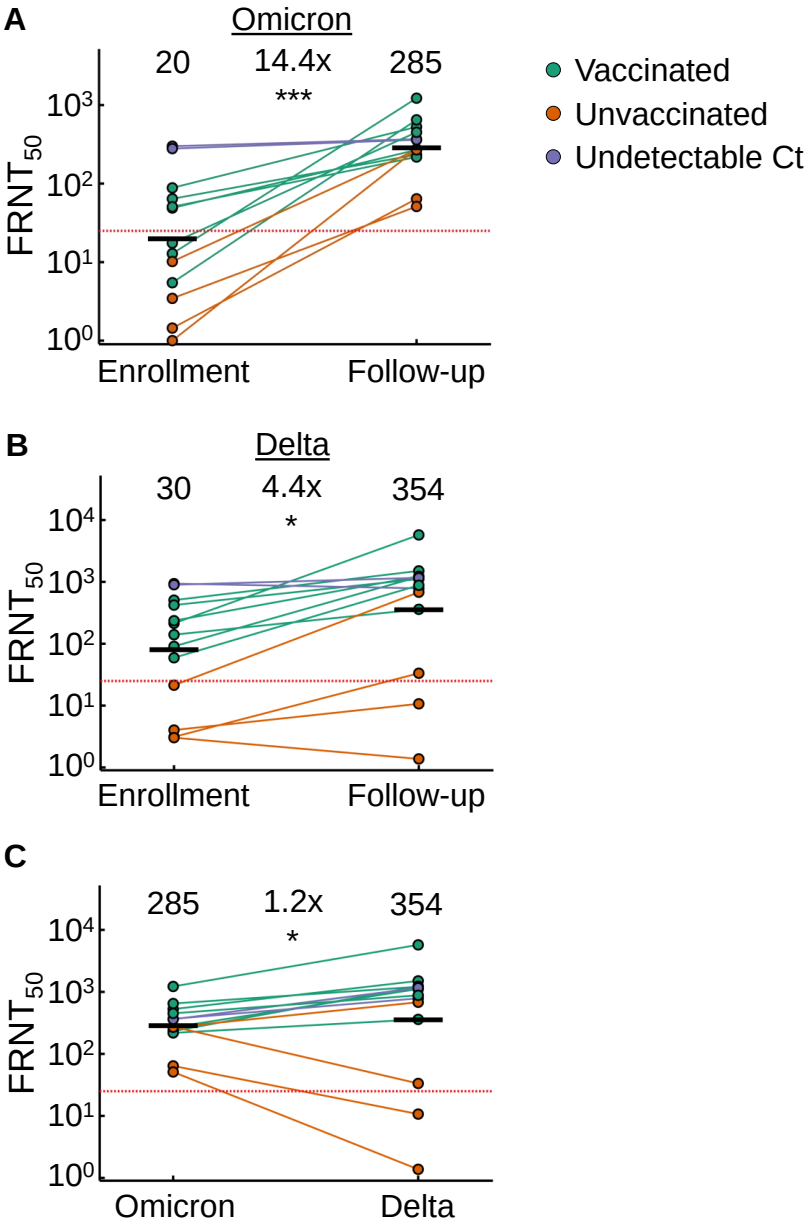

Figure 1: Enhancement of Delta neutralization by Omicron infection. (A) Omicron (A) or Delta (B) virus neutralization by blood plasma from n=13 participants infected in the Omicron infection wave at enrollment (median 4 days post-symptom onset) and at follow-up (median 14 days post-enrollment). (C) Comparison of neutralization activity against Omicron and Delta virus at follow-up. Participants were either previously vaccinated (green) or not (orange). Two participants (unvaccinated) with undetectable SARS-CoV-2 at enrollment are marked in purple. Numbers are geometric mean titers (GMT) of the reciprocal plasma dilution ($FRNT_{50}$) resulting in 50% reduction in the number of infection foci. Red horizontal line is most concentrated plasma used. p=3.6 $\times 10^{-4}$ for (A), p=0.016 for (B), and p=0.045 for (C) as determined by the Wilcoxon rank sum test.

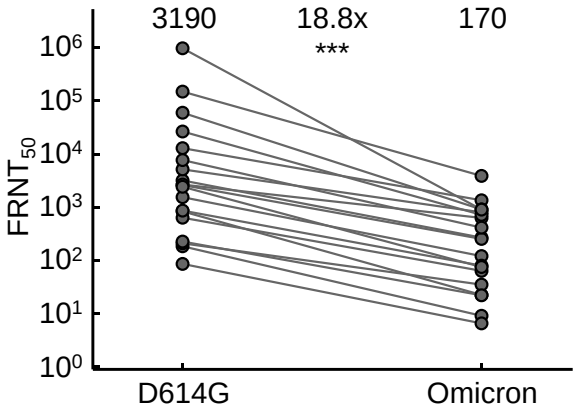

Figure S1: Neutralization of Omicron without R346K by Pfizer BNT162b2. Neutralization Omicron virus compared to D614G ancestral virus in participants vaccinated with BNT162b2.Samples were tested from n=19 participants, where n=6 were vaccinated and n=13 were vaccinated and previously infected, as described in Cele et al., Nature doi: https://doi.org/10.1038/d41586-021-03824-5. Numbers in black above each virus strain are GMT FRNT$_{50}$. Red horizontal line is most concentrated plasma used. p=2.3 $\times 10^{-4}$ by the Wilcoxon rank sum test.

Table S1: Participant details

Participant	Age	Sex	Vaccine	Symptoms date	Ct enrollment	Seq. confirmed
1	30-40	M	J&J	December	25	Yes
2	30-40	M	J&J	November	14	Yes
3	50-60	F	Pfizer	December	17	Yes
4	30-40	M	None	December	18	Yes
5	30-40	F	J&J	December	31	Yes
6	20-30	F	None	December	28	Yes
7	30-40	F	J&J	December	24	Yes
8	30-40	M	Pfizer	November	32	Yes
9	20-30	F	None	November	UND	
10	40-50	F	None	December	32	Yes
11	20-30	F	Pfizer	December	23	Yes
12	20-30	M	None	December	30	
13	20-30	F	None	December	UND	Yes

Ct: Cycle threshold by qPCR. Seq. confirmed: Verified Omicron by sequencing